SYNOPSIS

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"AYURVED BASED APPROACH IN CURATIVE MANAGEMENT OF DIABETES"

By

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Research Guide

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ABSTRACT:

It is even seen in practice that many patients suffer from various kinds of diabetic complications even their blood sugar is well under control. So a great deal of work is required in understanding the disease. Recent advances in modern health care delivery system indicate that insulin and other oral hypoglycemic agents are not able to check the diabetic complications. The hazardous side effects of the hypoglycemic agents after long term use have further created problems and hence an ideal therapy is still obscure.

INTRODUCTION:

It is clear that, development of insulin resistance and type two diabetes mellitus **(T2DM)** is multi-factorial and hence, it is quite possible that there will be variation in the incidence and intensity of this problem from region to region and there may be ethnic variations also. Depending on the presence of other risk factors and the degree of insulin resistance, the chances and rapidity of development of complications also increase in type two diabetes **(T2DM).** Hence, it is worthwhile looking for the prevalence of such risk factors in each population, since the manipulation by means of Ayurved system of medicine which will help us reduce the morbidity and mortality associated with type two diabetes **(T2DM)**. As there are no significant studies on this aspect from India where the incidence of type two diabetes and its complications are on the rise, this study is an attempt to draw some conclusion regarding the prevalence of hyper-insulinemial insulin resistance which both directly and indirectly, will accelerate the development diabetes and to evaluate curative aspect of diabetes by means of Ayurved system of medicine.

Though it is obvious from the above discussions that Ayurved system of medicine is an important affair in management of diabetes, it doesn't seem to have caught the attention of many. And as a result, there are not much of serious studies on the subject from this part of the world.

Insulin Resistance Syndrome **(IRS)** is identified as the biggest villain in the whole scenery of type two diabetes mellitus **(T2DM)**. But the prevalence of various components of the syndrome varies from place to place. Even the degree of hyper-insulinernia, which is an important consequential component of Insulin Resistance Syndrome **(IRS)** varies in different races and regions. **The data regarding this is lacking from India, which makes it difficult for us to understand the real extend of cardiovascular threat posed by T2DM. This**

study is an attempt in analyzing the prevalence of Insulin Resistance Syndrome (IRS) among type two diabetes mellitus (T2DM) and curative approach of it's by means of Ayurved system.

The metabolic syndrome, or pre-diabetes, is the fastest rising epidemic on the planet. This condition is characterized by: **OBESITY, INSULIN RESISTANCE, DYSLIPIDEMIA (Blood fats), HYPERTENSION, and HIGH INSULIN**. Insulin resistance most often goes undiagnosed. Hypertension is another epidemic, and **75%** of such people have diabetes. High blood cholesterol, and especially triglycerides, is characteristic. High blood insulin levels also go undiagnosed. Almost one in four Indian adults suffers from metabolic syndrome, and will soon be diagnosed with diabetes. Half of all diabetes goes undiagnosed. This is the fastest growing disease of all worldwide plain and simple India and other countries are also coping with growing epidemics. Type two diabetics **(T2DM)** (Non-insulin dependent) produce insulin, but the cells simply don't react well to it anymore. Here, the pancreas not only produces insulin, but usually overproduces it, since the effectiveness is so reduced. The best way to understand the dysfunction of insulin and blood sugar is the theory of *oxidative stress.* Here free radicals run rampant through the body, and use up our antioxidants - **Glutathione, SOD (Superoxide dismutase), Beta carotene, Vitamin - E, Vitamin- C, Melatonin, Lipoic acid**, and others. This is why it is so important to first of all lower the oxidative stress with better diet and exercise. Secondly, we need to take all the known antioxidant supplements to neutralize the excess free radicals. Scientists of the world are in basic agreement that free radical oxidative stress is central to blood sugar conditions. Any blood sugar dysfunction means poor quality of life and early death. The pancreas deteriorates, nerve damage of various kinds can be expected, liver disease is routine, and skin infections **(especially Staphylococcus)** are common. Your liver is central here since it produces the blood sugar from the food you eat. Your kidneys are the second most important organs. The list of side effects is almost endless, since the total health of the body is destroyed.

Eternity of Ayurveda cannot be denied by calling rudely unscientific without knowing its integrity and credibility and by unseeing profound proofs. **Research work is the integral part co-existing along with the sequential development of science knowingly or unknowingly. Ayurvedic science is nothing devoid of it.**

In Ancient treatise we find a vivid description of the disease solely attributed to metabolic derangement along with genetic predisposition. **Madhumeha** (Diabetes

mellitus) subtype of **Vataja Prameha** due to involvement of vital elements causes alarming health instability with higher prevalence. **Vata** is the conductor of healthy life and vitality supporter of all the embodied beings and sustains long life free of disorders. **Susruta** emphasized that **Vyan** and **Apana** vitiation causes **Sukra Dosa** and **Prameha**. Vyana because of its potential to perform the functions related to each and every body element and Apana due to its potential related with excretion. When we exploit Madhumeha (Diabetes mellitus) we cannot denied their credibility in the pathogenesis. This superior consideration of Susruta proved to be essential before profound treatment modality.

Changing life style, lack of exercise, fast foods, improper unbalanced diet, and sedentary life are showing upward trend in India. This has lead to the emergence of **Diabetes Mellitus** in the region. Iaterogenicity, genetic predisposition and degenerative changes proved fatal in diabetes mellitus. Recent **WHO** report revealed that in 1998, 135 million adult diabetics world wide and the figure is projected to reach **300 million up to by 2025, 20%** of the current global diabetic population resides in the South East Asia and India is one of the country in this region. **Considering all these facts the topic entitled "Ayurved based approach in curative management of diabetes" is selected for the proposed research work".**

REVIEW OF LITERATURE:

Pathophysiology of Diabetes as per Modern view

Insulin receptor:

Insulin receptor **(IR)** is a transmembrane tyrosine kinase, expressed as a tetramer in a 2a, 2P configuration **(Ebina et al., 1985; Ullrich et a1.1985).** The alpha subunit is presented to the exterior of the cell membrane and the beta subuit extends trans-membraneously to the interior of the cell. On secretion from pancreas, insulin rapidly reaches its receptor, the IR, which is widely expressed on the cells of various tissues where it interacts with its cognate receptor.

Action of insulin on its receptor:

Insulin binding to specific regions of the a-subunit leads to a rapid configurational change in the receptor that leads to autophosphorylation of specific Tyr residues of the intracellular region of the P-subunits through a transphosphorylation mechanism. This results inactivation of the Tyr kinase activity of the receptor **(Lee et al 1997)** . In the inactive state, the catalytic site of the Tyr kinase is occluded by the "activation-loop," preventing access of

ATP and various substrates **(Lee et al. 1997)**. The metabolic response to insulin is primarily mediated via the **P13-K** (Phosphatidyllnositol-3 Kinase) within kinase pathway. **(Czech and Corvera 1999)**. Stimulation of glycogen synthesis is another key metabolic effect of insulin. Glycogen synthase kinase-3 **(GSK-3)** mediates, at least in part, the activation of glycogen synthesis in response to insulin **(Cross et al. 1995).** Glycogen synthase kinase-3 **(GSK-3)** also inactivates the protein synthesis eukaryotic initiation factor (elF)-20 (the guanine nucleotide exchange factor) by phosphorylation. Insulin-mediated activation of Akt reverses these processes, thereby enhancing protein synthesis **(Welsh and Proud 1993)**.

Insulin Resistance:

Insulin resistance is a hallmark of type two diabetes **(T2DM)** that precedes and predicts the disease for several years **(Warram et al. 1990; Lillioja et a1. 1993; Juhan-Vague et al. 1993)**. About 80-90% of all type two diabetes **(T2DM)** coexists with insulin resistance **(Hochholdinger et al. 1999)** which usually also proceeds the first symptoms of the disease **(Zimmet et al. 2001; Alberti 2001)**. The prevalence of the insulin resistance syndrome has varied markedly between different studies, most likely because of the lack of accepted criteria for the definition of the syndrome **(DeFronzo 1988; Lillioja et a1.1988). There is abundant evidence that insulin resistance is a treatable precursor of type 2diabetes (T2DM) (Warram et al. 1990; Lillioja et al. 1993)** and perhaps of cardiovascular disease as well **(Reaven 1988; DeFronzo and Ferrannini 1991; Howard et al. 1996).** The latter association, which is independent of diabetes, may be partially a consequence of the relationship between insulin resistance and the "metabolic syndrome," which consists of obesity, particularly abdominal obesity; impaired glucose regulation; dyslipidemia of the high-triglyceride level-HDL cholesterol type; and hypertension**.(Defronzo and Ferrannini 1991 ; Stern et al. 1997).** Risk factors for Type 2 diabetes and atherosclerotic vascular disease such as insulin resistance, dyslipidemia, and hypertension cluster together in affected individuals **(John Cockeroft 2001)**.

Measurements of insulin resistance:

A number of techniques are available for making definitive measurements of insulin resistance, including the hyper insulinemic-euglycemic clamp technique, the frequently sampled intravenous glucose tolerance test, and the insulin suppression test. Although the HOMA-IR **(John Cockeroft et al. 2001)** has been the most widely used of these indexes, neither this nor any of the others has become the standard for diagnosing insulin resistance **(Anna Stears and Byrne 2001)**. These techniques however, are complicated, cumbersome, and in general, not suitable for large scale population studies or routine clinical work. For that

reason a wide variety of indexes based on simpler, clinical measurements have been proposed for assessing insulin resistance **(American Diabetes Association 2001).** There are evidences that fasting **TGL** (Triglyceride level) along with fasting insulin are variables that best predicted insulin sensitivity **(Kirsten Mcauley et al. 2001)**. A weighted combination of two routine laboratory measurements, i.e. fasting insulin and triglycerides, provides a simple means of screening for insulin resistance. **(Kirsten Mcauley et al., 2001).** Indexes of insulin resistance have acquired new salience with the development of various pharmaceutical agents, specifically metformin and the thiazolidinediones that sensitize the body to the action of endogenous insulin. Although initially developed for the treatment of diabetes, these agents also have a potential role in reducing the risk of diabetes and perhaps also of cardiovascular disease in insulin-resistant non-diabetic individuals. Moreover, the potential public health impact of such treatment could be large because it has been estimated that in developed countries as many as 25% of the non-diabetic population are as insulin resistant as patients with type 2diabetes **(Agha and lbrahim 1984).** Therapeutic reduction of insulin resistance has been shown to improve glycemic control **(Kipnes et al. 2001; Fonseca 2000)**.

Pathophysiology of Diabetes as per Ayurved System:

According to Sushruta, the excessive indulgence in the etiological factors related to Prameha results into Aparipakva Vata, Pitta, Kapha and Meda, which further proceed downward through the Mutravaha Srotasa to get localized at Basti Mukha and thus leading to disease Prameha **(Su. Ni. 6/4).** Dalhana interprets the term Aparipakva as Ama. Again he asserts that along with Aparipakva Vata, Rasa, Mamsa etc. should also be considered (Dalhana – Su. Ni. 6/4). Sushruta also asserted that, if all the Pramehas are treated improperly or ignored get terminated into Madhumeha **(Su. Ni. 6/27)**. Vagbhata narrated pathogenesis of Madhumeha very concisely. He indicated two types of pathogenesis i.e. Dahtukshayatmaka and Doshakshayatmaka. Further Charaka explained the pathogenesis in an elaborating manner i.e. general Samprapti of Prameha and specific Samprapti of Pramehas **(Ch. Ni. 4; Ch. Chi. 6/5-6)**. In medieval period mainly commentaries were written, but most of them content only the collection of thoughts from previous authors. MadhavaNidana: He collectively repeated the description of Charaka, Sushruta and Vagbhata **(Ma. Ni. 33)** Sharangadhara Samhita :Only mentioned the 20 types of Prameha in PrathAma Khanda 7th chapter. Bhavaprakasa: He described Prameha and Madhumeha along with some new herbomineral preparations **(Ma. Kh. 38th Chap)**.

OBJECTIVE OF THE STUDY:

- To evaluate curative aspect in diabetes management by means of various poly herbal, herbo-mineral preparations, diet regime, exercise, diabetes self-management education and support, lifestyle interventions, and goal setting by the way of Ayurved system of medicine.
- In the above circumstances, we are trying to identify whether fasting insulin alone or any of the other parameters can alone indicate the prevalence of insulin resistance in type 2 diabetes patients.
- Using the present study, we are trying to asses the degree of insulin resistance by way of measuring fasting plasma insulin levels and are trying to find out whether the insulin resistance reported using other criteria are in accordance with that measured using plasma insulin level.
- To evaluate Ayurved based approach in curative management of "Diabetes" patients in special reference to relationship between serum fasting insulin levels and markers of glycaemic control among diabetic patients.
- To measure the serum levels of fasting blood insulin, glucose, fructosamine and HbA1c in diabetic patients on treatment of modern system of medicine and Ayurved system of medicine individually.
- To relate the serum levels of fasting blood insulin, glucose, fructosamine and HbA1c in diabetic patients on treatment of modern system of medicine and Ayurved system of medicine individually.
- So this study is an attempt to assess the prevalence of a major component of this syndrome, i.e., the insulin resistance, by measuring fasting insulin in type 2 diabetic patients attending a major Ayurved hospital.
- An attempt to draw some conclusion regarding the prevalence of hyper-insulinemial insulin resistance which both directly and indirectly, will accelerate the development diabetes and to evaluate curative aspect of diabetes by means of Ayurved system of medicine.
- To reduce morbidity and mortality by improving adherence to important recommendations for preventing, detecting, and managing diabetic complications.

MATERIAL AND METHODS

Material

Analyzing botanical, phytochemical, pharmacognostical, pharmacological, toxicological and clinical evaluation of botanicals referred in special reference with curative aspect of diabetes In Ayurved system and formulating doses forms.

Source of data

The present study will be conducted in the Department of Botany, Yeshwant Mahavidyalaya, Nanded in collaboration with Sarvadnya Ayurved Hospital and K.K.Herbal Industries at Limbgaon, Nanded (Maharashtra) INDIA.

Method of collection of data

A. STUDY DESIGN: case control study.
B. STUDY PERIOD: January 2018 to January 2021.
C. PLACE OF STUDY: Dept. of Botany, Yeshwant Mahavidyalaya, Nanded in collaboration with Sarvadnya Ayurved Hospital and K.K.Herbal Industries at Limbgaon, Nanded (Maharashtra) INDIA.
D. SAMPLE SIZE: 100 cases. After screening of 1000 to 1200 patients.
E. INCLUSION CRITERIA

1. Age more than 18 years.
2. Patients with DM who have consented for the study.

F. EXCLUSION CRITERIA

1. Age less than18 years.
2. Patients taking insulin as a part of diabetes management.
3. Diabetes mellitus (Insulin Dependent).

G. METHODOLOGY

After obtaining clearance and approval from the Institutional Ethics Committee, type two diabetic patients satisfying the inclusion criteria (approximately 1000 to1200 patients) will be screened till the required sample size of cases and controls is obtained. Type two diabetes mellitus patients with known thyroid dysfunction will also be included in the study.

INTERNATIONAL STATUS:

The global prevalence of Type 2 Diabetes is expected to double in the period 2000-2025 and may reach a level of almost 300 million people (**King et al., 1998)**. It is reported that there will be a 57% increase in the prevalence of diabetes in Asia and a 24% increase in Europe from the year 2000 to the year 2010 (**Zimmet et al., 2001**). Diabetes mellitus, the most common metabolic problem, is responsible for the poor quality of life for many patients world over. They suffer from more cardiovascular problems and heart failure than the general population **(Paulo, 2005**). The severity of hyperglycemia is responsible only to a minor extend for this increased prevalence of cardiac problems (**Ake and Thomas, 2005**).

STATUS IN INDIA

Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively. **Prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India**. It is predicted that by 2030 diabetes mellitus may afflict up to **79.4 million** individuals in India. Indian population currently faces an uncertain future in relation to the potential burden that diabetes may impose upon the country. Many influences affect the prevalence of disease throughout a country, and identification of those factors is necessary to facilitate change when facing health challenges. So which factors are currently affecting diabetes in India that are making this problem so extreme? The etiology of diabetes in India is multi factorial and includes genetic factors coupled with environmental influences such as obesity associated with rising living standards, steady urban migration, and lifestyle changes. Yet despite the incidence of diabetes within India, there are no nationwide and few multi centric studies conducted on the prevalence of diabetes and its complications.

SIGNIFICANCE OF THE STUDY:

The prevalence of diabetes is approximately twice in the urban than in rural areas. **One out of 7 persons** with diabetes in the World is lives in India which has the largest diabetic population. In spite of using oral hypoglycemic agents and insulin modern medicine

is least bother about the sedentary life style and improper diet, so struggling to provide better management to counteract the complications and to provide the better health.

Holistic approach of Ayurveda in regard to preventive, promotive and purificative measures with due consideration of appropriate diet management proved to be fruitful to provide better health to diabetics.

PROPOSED WORK PLAN

Year-wise Plan of work and targets to be achieved:

First Year Plan: Review of literature regarding objectives of proposed work plan with analyzing botanical, phytochemical, pharmacognostical, pharmacological, toxicological and clinical evaluation of botanicals referred in special reference with curative aspect of diabetes In Ayurved system and formulating doses form for clinical trials after approval of ethical committee.

Second Year Plan: Screening of diabetes patients for clinical trials with prior consent for involvement in research study with prior education about poly herbal, herbo-mineral preparations, diet regime, exercise, diabetes self-management education and support, lifestyle interventions, and goal setting by the way of Ayurved system of medicine. Also pathological, biochemical and clinical data will obtain prior for evaluation of preclinical status condition and trial conduction with data collection in prescribed format.

Third Year Plan: Trial conduction and data collection with data arrangement and analysis with biostatistical methods for analysis outcomes of proposed research work with arrangement in prescribed format with result and discussion.

REFERANCES:

- Agha M and lbrahim MT. Maximum likelihood estimation of mixtures of distributions. *J.* Royal Stat. Soc.,Series C **(1984)**; 33: 327 - 333.
- Ake Sjoholm, Thomas Nystrom. Endothelial inflammation in insulin resistance. Lancet **(2005)**; 12: 365- 610.

- Alberti KGMM and Zimmet PZ for the WHO Consultation. Definition, Diagnosis and Classification of Diabetes Mellitus, Provisional report of a WHO Consultation. Diab. Med. **(1998)**; 15: 539 - 553.
- Anna J. Stears and Christopher D. Byrne. Adipocyte Metabolism and The Metabolic Syndrome. Diabetes,Obesity And Metabolism **(2001)**; **2:** 7 - 18.
- Cross DA, Alessi DR, Cohen P, Andjelkovich M and Hemmings BA, Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. Nature **(1995)**; 378:785-789.
- Czech MP and Corvera S. Signaling mechanisms that regulate glucose transport. J. Biol. Chem. **(1999)**; 274: 1865 - 1868.
- DeFronzo RA. The triumvirate: B-cell, muscle, liver: a collusion responsible for NIDDM. Diabetes **(1988)**; 37:667 - 87.
- DeFronzo RA and Ferrannini E. lnsulin resistance.Amultifaceted syndrome responsible for NIDDM, obesity,hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care **(1991)** ; 14: 173 - 194.
- Ebina Y, Ellis L, Jarnagin K, Edery M, Graf L, Clauser E, Ou JH, Masiarz F, Kan YW and Goldfine IW. The Human IR cDNA: the structural basis for hormone-activated transmembrane signaling. *Cell* **(1985)**; 40: *747* - 758.
- Fonseca V, Rosenstock J, Patwardhan R and Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA* **(2000)**; 283: 1695 - 1702.
- Hochholdinger F, Baier G, Nogalo A, Bauer B, Grunicke HH and Uberall F. Novel membrane-targeted ERKl and ERK2 chimeras which act as dominant negative, isotype-specific mitogen-activated protein kinase inhibitors of Ras-Raf-mediated transcriptional activation of c-fos in NIH 3T3 cells. Mol. Cell Biol. **(1999)**; 19: 8052 - 8065.
- Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF and Spiegelman BM. IRS-l-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-a and obesity-induced insulin resistance. Science **(1996)**; 271:665 - 668.
- John R. Cockeroft et al. Multiple Risk Factor Intervention in Type 2 Diabetes: An opportunity not to be missed. Diabetes, Obesity and Metabolism **(2001)**; 1: 10 - 17.

- Juhan-Vague I, Thompson SG and Jespersen **J,** Involvement of the hemostatic system in the insulin resistance syndrome: a study of 1500 patients with angina pectoris: the ECAT Angina Pectoris Study Group. Arterioscl. Thromb. **(1993)**; 13: 1865 -1 873.
- King H, Aubert R E and Herman W H. Global Burden of Diabetes 1995-2025: Prevalence, Numerical Estimates and Prjections, Diabetes Care **(1998)**; 21: 1414-1431.
- Kipnes MS, Krosnick A, Rendell MS, Egan JW, Mathisen AL and Schneider RL. Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. Am. *J. Med. (* **2001)** ; 1 l **l** : 10 - 17.
- Kirsten A. McAuley, Sheila M. Williams, Jim I. Mann, Robert J. Walker, Nick J. Lewis Barned, Lara A.Temple and Ashley W. Duncan, Diagnosing Insulin Resistance in the General Population. *Diabetes Care* **(2001)**; 24: 460 - 464.
- Lee J, Pilch PF, Shoelson SE and Scarlata SF. Conformational changes of the IR upon insulin binding and activation as monitored by fluorescence spectroscopy. Biochemistry **(1997)**; 36: 2701 - 2708.
- Lillioja S, Mott DM, Howard BV, Bennett PHI Yki-Jarvinen H, Freymond D, Nyomba BL, Zurlo F, Swinburn B and Bogardus C. Impaired glucose tolerance as a disorder of insulin action: longitudinal and crosssectional studies in Pima Indians. N. Engl. ***J.*** Med.**(1988)**; 318: 1217 - 1225.
- Lillioja S, Mott DM, Spraul M, Ferr a ro R, Foley JE, Ravussin E, Knowler WC, Bennett PH and Bogardus C.Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetesmellitus: prospective studies of Pima Indians. N. Engl. *J.* Med. **(1993)**; 329: 1988 - 1992.
- Paulo J. Oliveira. Cardiac Mitochondrial Alterations Observed in Hyperglycaemic Rats What Can We Learn From Cell Biology? Current Diabetes Reviews **(2005)**; 1: 11 - 21 11.
- Premalatha G, Santhi Rani CS, Deepa E, Rema M and Mohan V. Prevalence of Diabetic Complications in South Indians-The Chennai Urban Population study; Novo Nordisk Diabetic Update **(2000)**; 59 - 63.
- Ramachandran Ambadi, Chamukuttan Snehalatha, and Vijay Viswanathan. Explosion of Type 2diabetes in the Indian subcontinent. International Diabetes Monitor **(2003)**; 15(5): 1- 6.

- Reaven G. Banting Lecture 1988: Role of lnsulin Resistance in Human Diseases. Diabetes **(1988)**; 37: 1595 - 1607.
- Stern MP, Alberti KGMM, DeFronzo RA and Zimmet P, Eds. Chichester, U.K., John Wiley and Sons. The insulin resistance syndrome. In International Textbook of Diabetes Mellitus. 2nd ed. **(1997)**; 255 - 283.
- Warram JH, Martin BC, Krolewski AS, Soeldner JS and Kahn R. Slow glucose removal rate and hyperinsulinemia precede the development of type 2 diabetes in the offspring of diabetic parents. Ann Intern Med **(1990)**; 1 13: 909 - 91 5.
- Welsh GI and Proud CG. Glycogen synthase kinase-3 is rapidly inactivated in response to insulin and phosphorylates eukaryotic initiation factor elF-2B. Biochem J **(1993)**; 294: 625 - 629.
- Zimmet P, Alberti KG and Shaw J. Global and societal implications of the diabetes epidemic. Nature **(2001)**;414: 782 - 787.

SAMHITA:

- Madhava: Madhava Nidana with "Madhukosha Vyakhya", edited by Vaidya Sudarshana Shastri, Chaukhambha Sanskrit Sansthan, Varanasi. Orientalia, 5th edition, **(1992).**
- Sushruta : Sushruta Samhita with Dalhan's "Nibandha Sangraha" and Gayadas's "Nyaya-Chandrika" commentaries, Chaukhambha
- Vriddha Vagbhata : Ashtanga Sangraha with Indu's commentary, edited by Vaidya Ananta Damodar Aathawale, Pune, **(1980).**
- Vagbhata : Ashtanga Hridaya with Arundatta's "Sarvangasundari" and Hemadri's "Ayurveda Rasayana" commentaries edited by Vaidya Harishankar Paradkara, Chaukhambha Press, Varanasi **(1982).** Charaka: Charaka Samhita with commentary of Chakrapanidatta, edited by Vaidya Yadavaji Trikamji Acharya, Munshiram Manoharlal Publishers, Varanasi **(1981).**

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